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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/434,345	11/05/99	BOULIKAS	

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EXAMINER	
NGUYEN, T	

ART UNIT	PAPER NUMBER
1632	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/434,345	Applicant(s) BOULIKAS, TENI	
	Examiner Dave Nguyen	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *24-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2,3,7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

A new examiner has been assigned to examine this instant application.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-19), in the response filed May 21, 2001 is acknowledged.

The traversal is on the ground(s) that:

1) Group I claims and Group II claims are not distinct, that the claims of Group II cannot be practiced without practicing the invention of Group I, that a search of the art for references related to the subject matter of the claims of Group I may likely uncover references related to the subject matter of Group II, and that a serious burden has not been established by the examiner.

Applicant's traversal as to 1) is found persuasive to the extent that the Group I claims and claims 20-23. However, claims 24-26 are directed to a combination of cancer therapy by using a liposomal entrapped cisplatin and gene therapy for cancer therapy, which claims are directed to distinct classes and subclasses, *e.g.,* Class 514, subclass 44 and Class 424. In addition, a combination of gene therapy and chemotherapeutic treatment, as claimed in claims 24-26, at minimum includes a combination of method steps and material that is not claimed in group I claims, and thus, when employed as a whole, is distinct from that of Group I claims. Since Group I claims do not claim a combination gene therapy as claimed in claim 24-26 of Group II, a search of Group I claims does not necessarily overlap with that of Group II claims. Further, the materials and/or methods steps employed in the gene therapy method steps as recited in claims 24-26 are distinct and generates distinct function and/or effect, and thus, requires a serious burden from the examiner to examine for patentability.

Thus, the restriction of Group I claims and claims 24-26 of Group I is proper and therefore made final.

Claims 24-28 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Elected claims 1-23 are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Applicant's claimed invention encompasses a targeted therapy for targeting an effective amount of the encapsulated cisplatin of claims 16 and 17 to any solid tumor or metastasis. It is apparent that the encapsulated cisplatin of claims 16 and 17 does not even required to have any product and/or material so as to target the encapsulated cisplatin to a desired tumor site. Neither the prior art of record nor the as-filed specification teaches that the encapsulated cisplatin is capable of targeting only solid tumors or metastases. In fact, the specification on page 2, for example, teaches that cisplatin is toxic and does not discriminate non-tumor tissues from tumor tissues. Thus, it is not apparent as to how one skilled in the art, without any undue experimentation, would have been able to employed the claimed encapsulated cisplatin as a targeted therapy by intravenous administration to target only solid tumors or metastases, particularly on the basis of applicant's disclosure and the prior art of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 7-21 and 23 are rejected under 35 USC 103(a) as being unpatentable over Szoka (US Pat No. 5,567,434) taken with Perez-Soler *et al.* (US Pat No. 5,843,475) and Abra *et al.* (US Pat No. 6,126,966).

Szoka teaches a cancer therapy method of employing a liposome entrapping cisplatin (column 18, claim 2) prepared by a method comprising the use of any suitable lipid known in the art that is capable of forming liposomal micelles, *e.g.*, DMPG (column 4), and of an organic solvent comprising an alcohol including ethanol (column 3, column 17), wherein the ratio of compound (cisplatin) to lipid used preferably ranges from about 1:1 to about 1:20 (column 5). Administration routes including intravenous administration for use in cancer therapy are also disclosed on column 6.

Szoka does not teach explicitly a specific combination of a phosphatidyl glycerol lipid derivative and cisplatin (claim 1), nor does Szoka teaches the step of mixing a lipid/cisplatin mixture with at least 30% ethanol solution to form cisplatin micelles (claim 2), nor does Szoka

teaches the an addition of a hydrophilic polymer/lipid complex as a stabilizer to the cisplatin micelles including the use of PEG-DSPE, PEG-DSPC, hyaluronic acid-DSPE (claim 13), liposomes composed of cholesterol, HSPC and PEG-HSPC or PEG-DSPE (claim 11).

However, at the time the invention was made, Perez-Soler *et al.* teach that a liposome made of cisplatin/DMPG is effective for use as a liposomal antitumor composition (entire document, especially column 2).

In addition, Abra *et al.* teach that a liposomal composition containing an entrapped cisplatin compound which is composed of a vesicle-forming lipid derivatized with a hydrophilic polymer (PEG), and/or cholersterol, and/or HSPC is effective for use to increase the stability of cisplatin during its *in vivo* delivery to a tumor site (claim 1, columns 5 through 6, columns 9-12). In addition, column 9 bridging column 10 discloses the step of mixing a lipid/cisplatin mixture with at least 30% ethanol solution to form cisplatin micelles.

It would have been obvious for one of ordinary skill in the art to have employed a liposome made of cysplatin/any known phosphatidyl glycerol lipid derivative as a liposomal antitumor composition. One of ordinary skill in the art would have been motivated to have employed the liposome entrapping a cisplatin compound because Szoka teaches a cancer therapy method of employing a liposome entrapping cisplatin (column 18, claim 2) prepared by a method comprising the use of any suitable lipid known in the art that is capable of forming liposomal micelles, *e.g.,* DMPG (column 4), and of an organic solvent comprising an alcohol including ethanol (column 3, column 17), wherein the ratio of compound (cisplatin) to lipid used preferably ranges from about 1:1 to about 1:20 (column 5), and because Perez-Soler *et al.* teach that a liposome made of cisplatin/DMPG is effective for use as a liposomal antitumor composition.

It would also have been obvious for one of ordinary skill in the art to have further employed a suitable lipid, *e.g.,* cholesterol, DSPE and/or HSPC, and a hydrophilic polymer as stabilizer complexes to enhance the stability of the liposome of Szokan taken with Perez-Soler *et al.* One of ordinary skill in the art would have been motivated to have employed the stabilizer complexes in the liposomes of the combined cited references because Abra *et al.* teach that a liposomal composition containing an entrapped cisplatin compound which is composed of a

vesicle-forming lipid derivatized with a hydrophilic polymer (PEG), and/or cholersterol, and/or HSPC is effective for use to increase the stability of cisplatin during its *in vivo* delivery to a tumor site (claim 1, columns 5 through 6, columns 9-12).

It would also have been obvious as a matter of design choice for one of ordinary skill in the art to have employed the step of mixing a lipid/cisplatin mixture with at least 30% ethanol solution to form cisplatin micelles, particularly since it is common and routine in the prior art, as exemplified by Abra *et al.,* for a skilled artisan to have employed the step of mixing a lipid/cisplatin mixture with at least 30% ethanol solution to form cisplatin micelles.

Thus, the claimed invention as a whole was *prima facie* obvious over the prior art.

Claims 9, 13, 16, 17 and 19-21 are rejected under 35 USC 103(a) as being unpatentable over Szoka (US Pat No. 5,567,434) taken with Perez-Soler *et al.* (US Pat No. 5,843,475), Abra *et al.* (US Pat No. 6,126,966), and further in view of Unger *et al.* (US Pat No. 6,028,066).

The combined cited references of Szoka taken with Perez-Soler *et al.* and Abra *et al.* teach the encapsulation method of claim 9 as indicated above.

To the extent that the combined cited references do not teach explicitly the use of hyaluronic acid - DSPE in the method, it would have been obvious for one of ordinary skilled in the art to have incorporated any glycosaminoglycan including hyaluronic acid in any of the lipid stabilizer complex taught by the combined cited references, particularly glycosaminoglycan is routinely employed in the prior art to increase the stabilization and antithrombic properties of the lipid complexes. One of ordinary skill in the art would have been motivated to have employed including hyaluronic acid in any of the lipid stabilizer complex taught by the combined cited references because of the reasons set forth in the immediately preceding sentence and because Unger *et al.* teach that lipid complexed with hyaluronic acid can be used a stabilizer in any liposomal delivery composition (column 23, last paragraph).

Thus, the claimed invention as a whole was *prima facie* obvious over the prior art.

Claims 1, 2 and 5 are rejected under 35 USC 103(a) as being unpatentable over Szoka

(US Pat No. 5,567,434) taken with Perez-Soler *et al.* (US Pat No. 5,843,475), Abra *et al.* (US Pat No. 6,126,966), and further in view of Lee *et al.* (US Pat No. 5,908,777).

The combined cited references of Szoka taken with Perez-Soler *et al.* and Abra *et al.* teach the encapsulation method of claims 1 and 2 as indicated above.

To the extent that the combined cited references do not teach explicitly the use of a fusogenic peptide derivatized with a string of 1-6 negatively-charged amino acids at the N or C-terminus so as to enable the electrostatic binding to positively charged cisplatin/lipid complex in an aqueous solution entrapped in the liposomal composition, Lee *et al.* teach that a lipidic complex containing a fusogenic peptide enhances the fusion and delivery of the lipid complex through cell membrane of a target cell (column 7 citing Haensler and Szoka), and that fusogenic peptide can be derivatived by adding a string of negatively-charged amino acids (glutamic acid residues) at the N or C-terminus of the petide so as to enable the electrostatic binding to positively charged cisplatin/lipid complex in an aqueious solution (column 7).

It would have been obvious for one of ordinary skill in the art to have further employed a fusogenic peptide derivatized with a string of 1-6 negatively-charged amino acids at the N or C-terminus so as to enable the electrostatic binding to positively charged cisplatin/lipid complex in an aqueous solution. One of ordinary skill in the art would have been motivated incorporate a fusogenic peptide fusogenic peptide derivatized with a string of 1-6 negatively-charged amino acids at the N or C-terminus as a ionic complex with the cisplatin/lipid micelles of the combined cited references because Lee *et al.* teach that a lipidic complex containing a fusogenic peptide enhances the fusion and delivery of the lipid complex through cell membrane of a target cell (column 7 citing Haensler and Szoka), and that fusogenic peptide can be derivatived by adding a string of negatively-charged amino acids (glutamic acid residues) at the N or C-terminus of the petide so as to enable the electrostatic binding to positively charged cisplatin/lipid complex in an aqueious solution.

Thus, the claimed invention as a whole was *prima facie* obvious over the prior art.

Claims 1, 2, 5 and 6 are rejected under 35 USC 103(a) as being unpatentable over

Szoka (US Pat No. 5,567,434) taken with Perez-Soler *et al.* (US Pat No. 5,843,475), Abra *et al.* (US Pat No. 6,126,966), and further in view of Lee *et al.* (US Pat No. 5,908,777) and Gebeyehu *et al.* (US Pat No. 5,334,761).

The rejection of claims 1, 2 and 5 as being unpatentable over Szoka taken with Perez-Soler *et al.* Abra *et al.*, and further in view of Lee *et al.* is applied here as indicated above. To the extent that the combined cited references do not teach the use of a cationic lipid/DOPE complex as an additional fusogenic substance so as to enhance the transport of the cisplatin/lipid complex of the combined cited references, Gebeyehu *et al.* is one of many exemplified references that teach that cationic lipid/DOPE complex due to its enhanced affinity to cell membrane are routinely employed in the prior art to enhance the delivery of bioactive compounds across the cell membrane of a target cell (entire document, abstract, column 1, column 4).

It would have been obvious for one of ordinary skill in the art to have further employed any suitable cationic lipid/DOPE complex in the combined cisplatin/lipid/fusogenic peptide complex as taught by Szoka taken with Perez-Soler *et al.* Abra *et al.*, and further in view of Lee *et al.* One of ordinary skill in the art would have been motivated to have added any suitable cationic lipid/DOPE complex in the combined cisplatin/lipid/fusogenic peptide complex because Gebeyehu *et al.* is one of many exemplified references that teach that cationic lipid/DOPE complex due to its enhanced affinity to cell membrane are routinely employed in the prior art to enhance the delivery of bioactive compounds across the cell membrane of a target cell (entire document, abstract, column 1, column 4), and because one would have expected that the addition of a fusogenic cationic lipid/DOPE complex would further generate an additive fusogenic effect so as to enhance the delivery of the cisplatin compound to target tumor cells.

Thus, the claimed invention as a whole was *prima facie* obvious over the prior art.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2 and claims dependent therefrom are indefinite in the recitation of "range of 1:1 to 1:2" because it is not apparent as to what is exactly the criteria to identity the ratio of "1:1 to :1:2" To what physical characteristic(s) does the ratio of "1:1 to :1:2" represent? Clarification is requested.

Claim 11 is indefinite in the recitation of a non-proper Markush group. The recitation of "composed o cholesterol 10-60%, ... and....or...,.... and PEG-DSPE" renders the metes and bounds vague and indefinite.

Claim 23 is indefinite in the recitation of "the cell membrane of a tumor" because while a tumor cell does have a cell membrane, a tumor *per se* consists of a collection of tumor cells, each of which has its own membrane. Clarification is requested. In addition, the claim is indefinite because the claim refers the method of claim 7, however, claim 7 is directed to a product by process.

Claims 11 and 12 are rejected in the recitation of percent of a number wherein it is not apparent as to what is exactly the element, *e.g.,* weight, volume, the percentage represents.

Claims 16 and 17 are objected because the claim lacks an article -- A -- at the beginning of the claims so as to conform with US standard of a patent issued claim.

No claim is allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Kimberly Davis, whose telephone number is **(703) 305-3015**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Clark*, may be reached at **(703) 305-4051.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Patent Examiner
Art Unit: 1633

DAVE T. NGUYEN
PRIMARY EXAMINER